(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 October 2015 (01.10.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/145462 A1

(51) International Patent Classification:
*A61K 9/50* (2006.01) *A61K 9/20* (2006.01)
*A61K 31/4439* (2006.01) *A61K 9/48* (2006.01)
*A61K 9/16* (2006.01)

(21) International Application Number:
PCT/IN2015/000142

(22) International Filing Date:
26 March 2015 (26.03.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1042/MUM/2014 26 March 2014 (26.03.2014) IN

(71) Applicant: **CADILA HEALTHCARE LIMITED** [IN/IN]; Zydus Tower, Satellite Cross Roads, Ahmedabad - 380015, Gujarat (IN).

(72) Inventors: **KULKARNI, Sushrut, Krishnaji**; Sarkhej-Bavla N.H. No. 8A, Moraiya, Tal. Sanand, Dist. Ahmedabad - 382210, Gujarat (IN). **HANDA, Ajaykumar**; Sarkhej-Bavla N.H. No. 8A, Moraiya, Tal. Sanand, Dist. Ahmedabad - 382210, Gujarat (IN). **BAHETI, Sagar, Jugalkishor**; Sarkhej-Bavla N.H. No. 8A, Moraiya, Tal. Sanand, Dist. Ahmedabad - 382210, Gujarat (IN).

(74) Agents: **SUBRAMANIAM, Hariharan** et al.; Subramaniam & Associates, Central Square, Suite-328, Plaza III, 20 Manoharlal Khurana Marg, Bara Hindu Rao, (off Rani Jhansi Road), Delhi - 110006 (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17**:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

**Published**:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2015/145462 A1

(54) Title: PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN

(57) Abstract: The present invention relates to pharmaceutical compositions comprising a first component comprising dabigatran or a pharmaceutically acceptable salt thereof in the form of a tablet and a second component comprising an organic acid. The invention also relates to processes for the preparation of such compositions and using those compositions to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

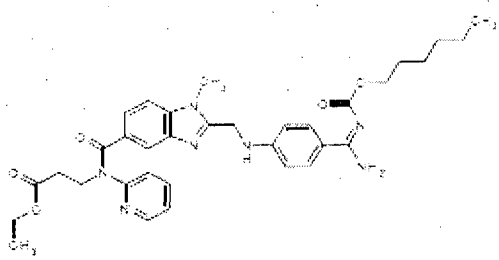
# PHARMACEUTICAL COMPOSITIONS OF DABIGATRAN

## FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions comprising a first component comprising dabigatran or a pharmaceutically acceptable salt thereof in the form of a tablet and a second component comprising an organic acid. The invention also relates to processes for the preparation of such compositions and using those compositions to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

## BACKGROUND OF THE INVENTION

Dabigatran etexilate is known as (3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridine-2-yl-amino]-propionic acid ethyl ester) and it has the following chemical structural formula:



Dabigatran etexilate is already known from PCT Publication No. WO 1998/37075, which discloses compounds with a thrombin-inhibiting effect and the effect of prolonging the thrombin time.

The solubility of dabigatran in water is only 1.8 mg/ml. Moreover, dabigatran has a strong pH-dependent solubility that is greatly increased in the acidic environment.

This leads to the problem that conventional oral pharmaceutical compositions have large variations in the bioavailability since the solubility of the active ingredient depends on the pH value in the patient's stomach. This is particularly problematic with patients in whom the stomach pH value is changed by physiological variability, illness, or premedications (for example, proton pump inhibitors).

PCT Publication No. WO 2005/018615 discloses a tablet comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof; one or more pharmaceutically acceptable organic acids with solubility in water of more than 1 g/250ml at 20°C and a pharmaceutically acceptable excipient or filler. However, the presence of an organic acid in close contact with the active in a tablet composition, without any special steps taken to separate the two from each other, can make the active highly susceptible to hydrolysis in the presence of humidity.

PCT Publication No. WO 2003/074056 discloses a pharmaceutical composition comprising an active ingredient and one or more pharmaceutically acceptable organic acids having a water solubility of >1 g/250 ml at 20°C, wherein the active ingredient layer is applied on an organic acid core while spatially separating the organic acid and active ingredient by an insulating layer.

PCT Publication No. WO 2011/107427 discloses an oral pharmaceutical composition comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof, and an inorganic acidic excipient. The composition as described comprises mixing dabigatran with the inorganic acidic excipient and optionally compressing the mixture to tablets or filling the mixture into capsules.

PCT Publication No. WO 2013/110567 discloses an oral pharmaceutical composition comprising dabigatran etexilate or a pharmaceutically acceptable salt thereof, and at least one water soluble cyclodextrin agent as an excipient.

PCT Publication No. WO 2013/124340 discloses dabigatran etexilate compositions comprising a mixture of at least two types of particles and optionally at least one pharmaceutically acceptable excipient, wherein a) the first type of particles comprise the active agent; b) the second type of particles comprise at least one pharmaceutically acceptable organic acid; and c) optionally at least one type of particles are coated with a protective coating layer.

There exists a need to prepare alternate compositions of dabigatran etexilate that are stable, easy or convenient to prepare, less tedious or technologically demanding and provide the desired in vitro release and bioavailability.

The aim of the present invention is to provide an alternative solid composition, i.e., a pharmaceutical composition, for oral administration of dabiagtran etexilate or a pharmaceutically acceptable salt thereof, particularly dabigatran etexilate mesylate (dabigatran etexilate methanesulphonate) by providing a composition characterized by two components separating dabigatran and an organic acid.

## SUMMARY OF THE INVENTION

In one general aspect there is provided a pharmaceutical composition comprising:

a) a first component comprising dabigatran or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients; and

b) a second component comprising an organic acid;

wherein the first component is in the form of a tablet and wherein the composition is in the form of a capsule.

In another general aspect there is provided a pharmaceutical composition of dabigatran, wherein the second component is in the form of a tablet, granules, pellets or powder.

In another general aspect there is provided a pharmaceutical composition of dabigatran, wherein the organic acid has a solubility in water of more than 1 g/250ml at 20°C.

In another general aspect there is provided a pharmaceutical composition of dabigatran, wherein the organic acid comprises tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid, aspartic acid or hydrates or acid salts thereof.

In another general aspect there is provided a pharmaceutical composition of dabigatran, wherein the composition comprises dabigatran etexilate mesylate.

In yet another general aspect there is provided a composition of dabigatran comprising from about 50 mg to about 200 mg of dabigatran etexilate mesylate.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the pharmaceutical composition may further include one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may include one or more fillers, binders, disintegrants, surfactants, lubricants, glidants, anti-tacking agents, plasticizers, and the like.

In another general aspect there is provided a pharmaceutical composition wherein the first component is substantially free of an organic acid.

In another general aspect there is provided a pharmaceutical composition, wherein the second component is substantially free of dabigatran.

In yet another general aspect there is provided a pharmaceutical composition comprising:

a) a first component comprising dabigatran etexilate mesylate; and

b) a second component comprising an organic acid; and

wherein the second component further comprises a pH independent coating.

In yet another general aspect there is provided a pharmaceutical composition wherein the pH independent coating comprises acrylic or methacrylic polymers, copolymers, esters or derivatives thereof, or combinations thereof.

In another general aspect there is provided a pharmaceutical composition, wherein the first component is prepared by a process comprising:

a) mixing dabigatran with one or more pharmaceutically acceptable excipients,

b) granulating the mixture obtained,

c) drying the granules followed by blending, lubrication and compression to obtain the first component; and

d) optionally coating the first component.

In another general aspect there is provided a pharmaceutical composition, wherein the second component is prepared by a process comprising:

a) spraying the organic acid using coating agents and one or more pharmaceutically acceptable excipients to form a wet mass,

b) drying the wet mass to obtain granules; and

c) sieving the granules followed by blending and lubrication.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the pharmaceutical composition may further include one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may include one or more fillers, binders, disintegrants, surfactants, lubricants, glidants, anti-tacking agents, plasticizers, and the like.

In another general aspect there is provided a pharmaceutical composition of dabigatran, wherein the composition releases at least about 50% dabigatran within 10 minutes and at least about 90% dabigatran within 30 minutes after subjecting the composition to dissolution testing at pH 2.0 according to the USP basket method at 100rpm.

In another general aspect there is provided a pharmaceutical composition of dabigatran, wherein the composition retains at least 90% of the potency of dabigatran in the pharmaceutical composition after storing the composition at 40°C and 75% relative humidity for at least three months.

The details of one or more embodiments of the invention are set forth in the description below. Other features of the invention will be apparent from the description.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to an oral pharmaceutical composition of dabigatran etexilate or a pharmaceutically acceptable salt thereof as an active ingredient.

The oral pharmaceutical composition of the present invention is characterized by two components separating dabigatran and an organic acid. Surprisingly, dabigatran compositions can now be prepared by easy processing by incorporation of two

components in a capsule with the added advantage of chemical, physical and organoleptic stablility and no dabigatran degradation due to hydrolysis. The compositions of the invention also provide faster in-vitro dabigatran release.

The compositions of the present invention are stable, easy to prepare, and provide an in-vitro release of dabigatran similar to that of the currently marketed product "PRADAXA", dabigatran etexilate mesylate capsules.

For the purposes of this application, the term "dabigatran" includes dabigatran etexilate or any pharmaceutically acceptable salts or derivatives thereof, including polymorphs, hydrates, solvates or amorphous forms, preferably dabigatran etexilate mesylate.

The term "component" used throughout the specification refers to an active ingredient or an organic acid containing powder, particles, agglomerates, granules, pellets, microspheres, minitablets, microcapsules, tablets, cores, coats on tablets or any solid physical form known to the person skilled in the art.

In one embodiment, there is provided a pharmaceutical composition wherein the first component is substantially free of an organic acid. In particular, the first component comprises less than 5% organic acid, preferably less than 2% organic acid, more preferably less than 1% organic acid, and even more preferably 0% organic acid.

In another embodiment, there is provided a pharmaceutical composition, wherein the second component is substantially free of dabigatran. In particular, the second component comprises less than 5% dabigatran, preferably less than 2% dabigatran, more preferably less than 1% dabigatran, and even more preferably 0% dabigatran.

In one embodiment, the pharmaceutical compositions of the present invention comprise about 25 mg to about 500 mg of dabigatran, preferably about 50 mg to about 300 mg.

In another embodiment, dabigatran is present in an amount from about 5% by weight to about 75% by weight of the composition, more preferably from about 10% to about 60%, more preferably from about 15% to about 50% and even more preferably from about 20% to about 50% by weight of the composition.

In yet another embodiment, dabigatran is present in an amount from about 20% to about 80% by weight of the first component, more preferably from about 30% to about 75%, even more preferably from about 40% to about 70% by weight of the first component.

Particularly suitable organic acids include, but are not limited to tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid, aspartic acid and the like or combinations thereof including the hydrates and acid salts thereof.

In another embodiment, the organic acid is present in an amount from about 1% by weight to about 95% by weight of the composition, more preferably from about 10% to about 80%, more preferably from about 20% to about 70% and even more preferably from about 20% to about 50% by weight of the composition.

In yet another embodiment, the organic acid is present in the composition in an amount from about 30% to about 90% by weight of the second component, more preferably from about 40% to about 85%, even more preferably from about 50% to about 85% by weight of the second component.

The current invention describes a pharmaceutical composition wherein dabigatran and the organic acid are not in direct contact with each other.

Yet another embodiment describes a pharmaceutical composition wherein the two components comprising dabigatran in the form of a tablet and the organic acid separately, further comprise a coating layer to avoid the instance of direct contact between dabigatran and the organic acid. This coating layer may be applied on any or both of the components. The coating layer may be in an aqueous/non-aqueous solution or dispersion form or in powder form.

The term "coat" as used herein is defined to mean a coating substantially surrounding a core which provides desirable properties to the dosage form. As is clear to the person of skill in the art, the coat may serve several purposes, like protecting the dosage form from environmental conditions, such as light or moisture, providing esthetic or taste-masking properties to the dosage form, making the dosage form easier to swallow or to handle during the production process, or modifying the release properties of the dosage form, such that pharmaceutically active ingredient is released at a different rate from the coated core than from the uncoated core. One or more than one coat, with the same or different functions or properties, may be applied to a core. The term "coat" includes, but is not limited to, modified release coat, immediate release coat and non-functional soluble coat, pH dependent and independent release coat.

The pharmaceutically acceptable excipients may include one or more fillers, binders, disintegrants, surfactants, lubricants, glidants, anti-tacking agents, plasticizers, and the like.

Suitable fillers may include one or more of microcrystalline cellulose, starch, dibasic calcium phosphate, tribasic calcium phosphate, calcium carbonate, dextrose, kaolin,

magnesium carbonate, magnesium oxide; sugars such as lactose or sucrose; sugar alcohols such as mannitol, sorbitol, erythritol and the like. The filler may be present in an amount of 5 to 80% by weight of the composition.

Suitable binders may include one or more of hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carbomer, dextrin, ethyl cellulose, methylcellulose, shellac, zein, gelatin, polymethacrylates (eg. eudragit), polyvinylpyrrolidone, pregelatinized starch, sodium alginate, gums, synthetic resins, silicic acid, hydrophilic polymers and the like. The binder may be present in an amount of 2 to 60% by weight of the composition, more preferably in an amount of 2 to 40% by weight of the composition.

The term "hydrophilic polymer" comprises polymers with polar groups. Examples of polar groups are hydroxy, amino, carboxy, carbonyl, ethers, esters, and sulfonates. Hydroxy groups are particularly preferred. Examples of suitable hydrophilic polymers are cellulose derivatives, in particular hydrophilic derivatives of the cellulose (e.g. HPMC, HPC, carboxymethylcellulose, preferably as sodium or calcium salt, hydroxyethylcellulose, hydroxypropylcellulose), polyvinylpyrrolidone, preferably with a molecular weight of from 10,000 to 60,000 g/mol, copolymers of PVP, preferably co-polymers comprising vinylpyrrolidone and vinylacetate units (e.g. povidone, VA64, BASF), preferably with a molecular weight between 40,000 and 70,000 g/mol, poly(oxyethylene) alkyl ether, polyethylene glycol, co-block polymers of ethylene oxide, and propylene oxide (poloxamer, pluronic), derivatives of polymethacrylates, polyvinyl alcohol, polyvinyl alcohol derivatives, polyethylene glycol, and polyethylene glycol derivatives.

Suitable disintegrants may include one or more of croscarmellose sodium, sodium starch glycolate, low substituted hydroxylpropyl cellulose(L hydroxylpropyl cellulose), pregelatinized starch, sodium carboxymethyl cellulose, cross-linked

polyvinylpyrrolidone and the like. The disintegrants may be present in an amount of 0.5 to 20% by weight of the composition.

Suitable surfactants may include one or more of anionic, cationic, non-ionic or amphoteric surfactants or those known to the person skilled in the art. Non-limiting examples of surfactants include polyoxyethylene-polyoxypropylene co-polymers and block co-polymers, commercially available as Pluronic™ or Poloxamer™, ethoxylated cholesterins, commercially available as Solulan™ vitamin derivatives, e.g. vitamin E derivatives such as tocopherol polyethylene glycol succinate (TPGS), sodium dodecylsulfate or sodium lauryl sulfate; a bile acid or salt thereof, for example cholic acid, glycolic acid or a salt.

Suitable lubricants and glidants may include one or more of talc, metallic stearates such as magnesium stearate, calcium stearate, zinc stearate; colloidal silicon dioxide, finely divided silicon dioxide, stearic acid, hydrogenated vegetable oil, glyceryl palmitostearate, glyceryl monostearate, glyceryl behenate, polyethylene glycols, sodium stearyl fumarate, ; and the like. It would be appreciated that a person skilled in the art is cognizant of the fact that lubricant, glidant or anti-tacking agent may be used interchangeably. The lubricant, glidant or anti-tacking agent may be present in an amount ranging from 0.1 % to 15 % w/w of the composition.

Suitable plasticizers may include one or more of triacetin, diethyl phthalate, tributyl sebacate, polyethylene glycol and the like.

Suitable coating materials suitable for present application include but are not limited to cellulose derivatives such as hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer, ethyl cellulose, EUDRAGIT® RLPO, EUDRAGIT® RSPO, OPADRY® and the like. Preferred coating materials for second component comprise

pH independent, non-enteric acrylic or methacrylic polymers, copolymers, esters or derivatives thereof, or combinations thereof.

The pharmaceutical compositions as described herein may be prepared by processes known to the person having ordinary skill in the art of pharmaceutical technology such as direct compression, wet granulation, dry granulation or melt granulation.

The current invention encompasses process of preparing compositions of dabigatran, comprising a first component comprising dabigatran and one or more pharmaceutically acceptable excipients in the form of a tablet and a second component comprising an organic acid and one or more pharmaceutically acceptable excipients.

In one embodiment, the pharmaceutical composition of the present invention comprises a first component contained in a tablet characterized by the presence of dabigatran, and a second component characterized by the presence of an organic acid, wherein the composition is prepared by a process comprising:

a) determining specific amounts of the first and second components necessary to produce the final composition; and

b) incorporating the specified amounts of the components into the composition.

Another embodiment describes a pharmaceutical composition wherein the first component comprising dabigatran is in the form of a tablet and the second component comprising an organic acid is in the form of a tablet, granules, beads, pellets, powder, particles, agglomerates, microspheres, minitablets, microcapsules.

In another embodiment, there is provided a process for preparing the first component, wherein the component is in the form of a tablet, wherein the process comprises the steps:

a) mixing dabigatran with one or more pharmaceutically acceptable excipients,

b) granulating the mixture obtained in a granulator or by top spray granulation,

c) drying the granules followed by blending, lubrication and compression to obtain the first component; and

d) optionally coating the first component.

In another embodiment, there is provided a process for preparing the first component, wherein the component is in the form of a tablet, wherein the process comprises the steps:

a) mixing dabigatran with a diluent, a binder and a disintegrant and other suitable pharmaceutical excipients followed by compression to form the first component; and

b) optionally coating the first component.

In another embodiment, there is provided a process for preparing the second component, wherein the process comprises the steps:

a) top spraying the organic acid using coating agents and one or more other pharmaceutically acceptable excipients to form a wet mass,

b) drying the wet mass to obtain granules; and

c) sieving the granules followed by blending and lubrication.

In another embodiment, there is provided a process for preparing the second component, wherein the process comprises the steps:

a) blending at least one organic acid and at least one pharmaceutically acceptable excipient,

b) extruding the blend of step 'a' to form extrudates,

c) spheronizing the extrudates to form organic acid pellets; and

d) coating the organic acid pellets with a coating layer.

In another embodiment, there is provided a process for preparing the second component, wherein the process comprises coating the inert organic acid beads with a coating layer.

In another embodiment, there is provided a process for preparing the second component, wherein the process comprises the steps:

a) blending at least one organic acid and at least one pharmaceutically acceptable excipient,

b) granulating the blend of step 'a' with a binder solution to form organic acid granules; and

c) coating the granules with a coating layer.

Without being bound by any particular theory, the smoothness (or roughness) of the coating layer can enhance solvent evaporation from the surface and decreases the amount of surface residual solvent, in doing so reducing the amount of solvent which may cause organic acid leaching and possible interaction and subsequent degradation of dabigatran due to hydrolysis or other means.

The coating layer may provide a weight gain from about 5% to about 30%, more preferably, from about 10% to about 30% by weight of the organic acid beads.

In another embodiment, the required quantities of two components prepared by any of the above mentioned techniques may be compressed into a tablet, filled into pouches, encapsulated into a capsule of any desirable size, for example, a size 000, 00, 0el, 0, 1, 2, 3, 4, or 5 to provide a final dosage form.

Components of a suitable capsule shell include, but are not limited to, hydroxypropyl methylcellulose and gelatin. Preferably, a capsule shell is a hydroxypropyl methylcellulose (HPMC) shell. Typically, commercially available HPMC capsules

include small amounts of water, colorants (e.g., $TiO_2$ and iron oxides), and optionally gelling agents and gelling promoters. They have relatively low moisture content, making them suitable for moisture-sensitive materials. Such capsules resist breakage even at low moisture levels. However, the capsules of cellulose ether film suffer from the problem that the gelling aid which is blended for assisting in film formation will precipitate out on the film surface during long-term storage. During long-term storage of these cellulose ether film capsules, the water content of the film can be lowered owing to the storage environment or the water absorption of the fill. Then the potassium or calcium ions as the gelling aid re-form potassium chloride or calcium chloride which precipitates out on the film surface. Patent no. US 6,649,180 suggests means to overcome this problem by limiting the total content of alkoxyl and hydroxyalkoxyl groups in the cellulose ether to 37.6% by weight. More particularly, the total content corresponds to the total content of methoxyl groups (abbreviated as "MO groups") and hydroxypropoxyl groups (abbreviated as "HPO groups") in the case of HPMC is considered. However, surprisingly the compositions of the present invention were found to be physically and organoleptically stable during the entire stability conditions i.e., the capsule shells showed no signs of white precipitates. HPMC capsule shells used for the present invention preferably comprise methoxyl groups and hydroxypropoxyl groups combined of 23 to 39% by weight of the hydroxypropyl methyl cellulose; more preferably 30 to 39%, even more preferably 37 to 39% and still more preferably 37.7 to 39%.

In another embodiment, the compositions of the present invention provide a faster dabigatran release than available marketed composition, wherein it releases at least about 50% dabigatran within 10 minutes, more preferably at least about 60% dabigatran within 10 minutes; releases at least about 90% dabigatran within 30 minutes, more preferably at least about 95% dabigatran within 30 minutes after subjecting said composition to dissolution testing in 0.01N HCl (900ml) at pH 2.0 according to the USP basket method at 100rpm.

In further embodiment, the pharmaceutical compositions of the present invention are found to be stable and may retain at least 90% of the potency of dabigatran in the composition after storing the composition at 40° C and 75% relative humidity for at least three months.

In another embodiment, the pharmaceutical composition provides for a relative $AUC_{0-24h}$, $C_{max}$ and $C_{min}$ in the range of 80% to 125%, as compared to Pradaxa®, the currently marketed composition in the USA..

Another embodiment discloses a method for prophylaxis or treatment of venous and arterial thrombotic disease condition comprising orally administering to the subject a therapeutically effective amount of the composition of the present invention, wherein said condition is selected from a group consisting of deep leg vein thrombosis, reocclusion after a bypass operation or angioplasty, occlusion in peripheral arterial disease, pulmonary embolism, disseminated intravascular coagulation, coronary thrombosis, stroke, and the occlusion of a shunt or stent, systemic embolism in patients with non-valvular atrial fibrillation.

The invention is further illustrated by the following examples which are provided to be exemplary of the invention and do not limit the scope of the invention. While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention

**EXAMPLE 1**

TABLE 1

| S.N. | Ingredient | Mg/tablet |
|---|---|---|
| **First component** | | |
| Intra-granular | | |
| 1 | Dabigatran etexilate mesylate | 86.47 |
| 2 | Microcrystalline cellulose(101) | 9.50 |
| 3 | L- Hydroxypropyl cellulose | 10.00 |
| 4 | Sodium starch glycolate | 2.00 |
| 5 | Hydroxypropyl cellulose LF | 3.00 |
| 6 | Acetone | q.s |
| Extra-granular | | |
| 7 | Microcrystalline cellulose(102) | 11.10 |
| 8 | L- Hydroxypropyl cellulose | 10.00 |
| 9 | Sodium starch glycolate | 2.00 |
| 10 | Talc | 1.35 |
| 11 | Colloidal silicon dioxide | 0.67 |
| 12 | Hydrogenated castor oil | 2.70 |
| 13 | Magnesium stearate | 2.70 |
| Coating | | |
| 14 | Opadry | 3.50 |
| 15 | Isopropyl alcohol | q.s |
| 16 | Dichloromethane | q.s |
| **Second component** | | |
| 1 | Citric acid anhydrous | 97.00 |
| 2 | Eudragit RLPO | 16.36 |
| 3 | Talc | 8.19 |

| | | |
|---|---|---|
| 4 | Polyethylene glycol (PEG 6000) | 1.64 |
| 5 | Ilsopropylalcohol (IPA) | q.s |
| 6 | Acetone | q.s |
| 7 | Water | q.s |
| 8 | Talc | 0.81 |

PROCESS:

STEP I: FIRST COMPONENT:

Dabigatran etexilate mesylate, microcrystalline cellulose, L- Hydroxypropyl cellulose and sodium starch glycolate were mixed and granulated using a solution of hydroxypropyl cellulose LF in acetone in a granulator. The granules were dried, sized and blended with microcrystalline cellulose, L- hydroxypropyl cellulose, sodium starch glycolate. The blend was lubricated using talc, colloidal silicon dioxide, hydrogenated castor oil and magnesium stearate. The lubricated granules were compressed using suitable size punches.

STEP II: SECOND COMPONENT:

Citric acid anhydrous was top sprayed using eudragit, talc and PEG solution in IPA, acetone and water in a glatt. The wet granular mass was dried at a specified inlet temperature till specific moisture content was achieved. The dried granules were sized and lubricated with talc.

STEP III:

The required quantities of the first and the second component obtained were filled in capsules.

The dissolution performance for the composition was measured using a USP-I rotating basket apparatus. Release times were measured by placing the capsule in a

small wire basket placed on the end of a rod spinning at 100 rpm. Aliquots were withdrawn from pH 2.0 HCl buffer up to 1 hr.

Table 1a: Dissolution performance for the composition of Example 1.

| Medium | Time (Min) | % drug release |
|---|---|---|
| Ph 2.0; Medium: 0.01N HCl | 10 | 96.6 |
| | 15 | 99.4 |
| | 20 | 100 |
| | 30 | - |
| | 60 | - |

While the invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the invention.

**WE CLAIM:**

1. A pharmaceutical composition comprising:
   a) a first component comprising dabigatran or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients; and
   b) a second component comprising an organic acid;
   wherein the first component is in the form of a tablet and the composition is in the form of a capsule.

2. The pharmaceutical composition according to claim 1, wherein the second component is in the form of a tablet, granules, pellets or powder.

3. The pharmaceutical composition according to claim 1, wherein the organic acid comprises tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid, aspartic acid or hydrates or acid salts thereof.

4. The pharmaceutical composition according to claim 1, wherein the organic acid has a water solubility of more than 1 g/250ml at 20°C.

5. The pharmaceutical composition according to claim 1, wherein the composition comprises dabigatran etexilate mesylate.

6. The pharmaceutical composition according to claim 5, wherein the composition comprises from about 50 mg to about 200 mg of dabigatran etexilate mesylate.

7. The pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable excipients comprise one or more of fillers, binders, disintegrants, surfactants, lubricants, glidants, anti-tacking agents, and plasticizers.

8. The pharmaceutical composition according to claim 1, wherein the first component is substantially free of an organic acid.

9. The pharmaceutical composition according to claim 1, wherein the second component is substantially free of dabigatran.

10. The pharmaceutical composition according to claim 1, wherein the second component further comprises a pH independent coating.

11. The pharmaceutical composition according to claim 10, wherein the pH independent coating comprises acrylic or methacrylic polymers, copolymers, esters or derivatives thereof, or combinations thereof.

12. The pharmaceutical composition according to claim 1, wherein the first component is prepared by a process comprising:

a) mixing dabigatran with one or more pharmaceutically acceptable excipients,

b) granulating the mixture obtained,

c) drying the granules followed by blending, lubrication and compression to obtain the first component; and

d) optionally coating the first component.

13. The pharmaceutical composition according to claim 1, wherein the second component is prepared by a process comprising:

a) spraying the organic acid using coating agents and one or more pharmaceutically acceptable excipients to form a wet mass,

b) drying the wet mass to obtain granules; and

c) sieving the granules followed by blending and lubrication.

14. The pharmaceutical composition according to claim 1, wherein the composition releases at least about 50% dabigatran within 10 minutes and at least about 90% dabigatran within 30 minutes after subjecting the composition to dissolution testing at pH 2.0 according to the USP basket method at 100rpm.

15. The pharmaceutical composition according to claim 1, wherein the composition retains at least 90% of the potency of dabigatran in the pharmaceutical composition after storing the composition at 40°C and 75% relative humidity for at least three months.

16. The pharmaceutical composition according to claim 1, wherein the composition is in the form of a capsule wherein the capsule shell comprises hydroxypropyl methylcellulose with a content of methoxyl groups and hydroxypropoxyl groups combined of 37.7% to 39 % by weight of the hydroxypropyl methylcellulose.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2015/000142

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/50 A61K31/4439
ADD. A61K9/16 A61K9/20 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 2013/124340 A1 (ESTEVE LABOR DR [ES])<br>29 August 2013 (2013-08-29)<br>cited in the application<br>page 4, line 10 - page 5, line 24<br>page 6, line 1 - page 7, line 16<br>page 7, line 32 - page 9, line 7<br>page 10, line 34 - page 11, line 12<br>page 13, line 6 - page 15, line 20<br>examples<br>----- | 1-16 |

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 1 September 2015 | 08/09/2015 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | van de Wetering, P |

1

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2015/000142

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 2013124340 A1 | 29-08-2013 | AU 2013224146 A1 | 28-08-2014 |
| | | CA 2864423 A1 | 29-08-2013 |
| | | CN 104114158 A | 22-10-2014 |
| | | EP 2817000 A1 | 31-12-2014 |
| | | JP 2015511241 A | 16-04-2015 |
| | | KR 20140135216 A | 25-11-2014 |
| | | NZ 628301 A | 31-07-2015 |
| | | US 2015030680 A1 | 29-01-2015 |
| | | WO 2013124340 A1 | 29-08-2013 |